REMARKS

Applicant thanks Examiner Gambel for the telephonic discussions with the undersigned on July 21 and July 22, 2010 and believes the following to be correct:

(1) On September 23, 2009, the Office issued a Communication clearly stating that the Office Action dated April 3, 2009 was being withdrawn and that a new Office Action would be mailed shortly. In view of the Notice of Non-Compliant Amendment mailed July 15, 2010 and further in view of conversations with Examiner Gambel, it is clear that the Office is now treating the 9/23/09 Communication as merely having withdrawn the finality of the 4/3/09 Office Action.

(2) Applicant filed a response with claim amendments on June 2, 2009, which have been entered by Examiner Gambel.

(3) Applicant's supplemental response and claim amendments filed on December 2, 2009 have not been entered.

Accordingly, the claim amendments herein are based on the claims entered through the June 2, 2009 amendments: claims 1-18, 20-21, and 45-58 are pending. Claims 1-9 have been amended. Claims 19 and 22-44 were cancelled previously. Claims 51-58 have been added to reinstate cancelled claims 19, 22, 24, 25, 27, 28, 32, and 34, respectively. Neither the amendments nor the new claims introduce any new matter.

Applicant further notes that the pending claims are essentially the same as the claims entered through the Amendment and Response filed on December 8, 2008. To facilitate the review of the pending claims by Examiner Gambel, Applicant hereby submits supporting arguments as filed in that Amendment and Response, which address certain cited references. Further, Applicant re-submits the Declaration from Dr. Rick Wetsel that was filed with the Supplemental Response to Office Action dated December 2, 2009 but was not entered. As discussed in detail below, the Declaration further supports Applicant's position that the pending claims are patentable over the prior art. Applicant points out that the amendment filed June 2, 2009 resulted in a set of claims

drawn to subject matter which had not been rejected (other than for provisional double patenting) by the 4/3/09 Office Action and therefore should have been considered allowable. In the present amendment, in addition to that subject matter, claims to subject matter which had been rejected have been resubmitted (thereby making the claims essentially identical to the claims filed December 8, 2008) in view of the Declaration from Dr. Rick Wetsel which further supports the patentability of the resubmitted claims.

The following text is a supplemental response to the 4/3/2009 Office Action which is now considered by the Office to be the active document listing the outstanding rejections. It is requested that the Examiner base his examination on the claims and remarks submitted herein.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. Applicant acknowledges with appreciation that Applicant's submission filed on December 8, 2008 was entered and further (in response to the Notice of Non-Compliant Amendment mailed July 15, 2010) that Applicant's submission filed on June 2, 2009 has also been entered.

Election/Restriction

2. Applicant acknowledges that claims 23, 26, 29, 31, 33, 35, 41, 42, and 44 are withdrawn.

Double Patenting Rejection

3-4. Claims 1-22, 24, 25, 27, 28, 32, 34, and 45-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-14 of copending application no. 11/127,438. Once allowable subject matter has been identified in the present application, Applicant will evaluate the filing of a terminal disclaimer.

Rejections Under 35 U.S.C. § 103

5-7. Claims 1-10, 18, 22, 24, 25, 27, 28, 32, and 34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Drouin et al. (*J. Immunol.* (2001) 166:2025-2032). Claims 11-13, 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Drouin et al. as applied to claims 1-9 above and further in view of Fitch et al. (*Circulation* (1999) 100:2499-2506). Claims 17 and 45-48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Drouin et al. as applied to clams 1-9 above and further in view of U.S. Patent 4,228,795 to Babington.

The Office Action dated April 3, 2009 stated that based on the teachings of Drouin et al., it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the instant application was filed to treat subjects with asthma using an anti-C5 antibody. Applicant continues to respectfully disagree. The Drouin et al. reference does not disclose or suggest methods for using an anti-C5 antibody as instantly claimed.

The Office contends that the Drouin et al. reference discloses that C5a receptor (C5aR) ***is increased on bronchial epithelial and smooth muscle cells in sepsis and in asthma*** and that septic primates and rats treated with anti-C5a antibodies have reduced pulmonary edema and lung injury. However, as repeatedly noted by Applicant (e.g., in the Response dated December 8, 2008), this is based on an incorrect interpretation of the reference's teachings.

Specifically, Applicant and the Office differ in their interpretation of the meaning of the following passage of Drouin et al.: "Moreover, we have established that both receptors [C3a receptor (C3aR) and C5aR] are up-regulated in two distinct models of lung inflammation: endotoxemia and OVA-induced asthma." Drouin et al. at 2029, column 2. The Office interprets the passage as teaching that C5aR is upregulated in the OVA-induced asthma model and thereby providing sufficient reason for a skilled artisan to practice the claimed invention. In contrast, Applicant urges that the foregoing interpretation is flawed - that while the reference discloses that C3aR and C5aR are both upregulated in endotoxemia, the reference discloses only that C3aR, but not that C5aR, is upregulated in the OVA-induced asthma model.

Note that Applicant herein resubmits a Declaration by Dr. Rick Wetsel, the senior author of Drouin et al. and unarguably a skilled artisan at the time the application was filed, which Declaration unambiguously resolves the dispute in favor of Applicant. "[Applicant's] interpretation is correct." *See* Declaration at page 2, paragraph 6. Dr. Wetsel states that "[o]nly C3aR is upregulated in the OVA-induced asthma model and ... C5aR ***was not shown*** to be upregulated in the OVA-induced asthma model in the data presented in the above-cited Drouin et al. publication." *Id.* (emphasis added). Moreover, Dr. Wetsel further states that the above-cited passage of the reference he authored was intended only to be general, with the more detailed analysis of the data discussed on pages 2030 and 2031. *Id.* For example, in the first full paragraph on page 2031 of the reference he and his co-authors further clarified:

> In contrast to mice treated with LPS, C3aR and C5aR expression did not change on bronchial and alveolar epithelial cells from OVA-challenged lungs. However, bronchial smooth muscle expression of C3aR was increased in OVA-challenged mice relative to the saline controls. Although further study is required to determine the role of each receptor in these inflammatory models, ***these results suggest that both receptors contribute to lung function in the endotoxemia model, whereas C3aR may play a more significant role in lung inflammation in the asthma model***. Recent observations that OVA-challenged C3aR-deficient guinea pigs (65) and mice (66) have reduced bronchial hyperreactivity support the concept that C3aR may regulate bronchial smooth muscle function in this disease. (Emphasis added.)

In view of the foregoing, it is clear that the authors of Drouin et al. did not interpret their own results and reach the conclusions as stated in the 4/3/2009 Office Action. The Declaration underscores that the authors did not intend for their data to be interpreted in the way that the Office interpreted them. Accordingly, Applicant again respectfully submits that the basis for the obviousness rejection, as presented in the Office Action of April 3, 2009, is incorrect.

We further note that the prior art at the time of filing (and post-filing references) fail to suggest the benefits of using anti-C5 antibodies to treat asthma. A proper determination of *prima facie* obviousness requires that the Examiner consider ***all teachings in the analogous prior art*** and what the combined teachings would have suggested to the skilled artisan. It is recognized that

> [w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *See* MPEP § 2143.01 (II) citing *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

As evidence of the state of the art at the priority date of the application, we provide Karp et al. (2000) *Nature Immunology* 1(3):221 (referred to as Karp; also re-submitted herewith as Exhibit A), a reference published one year prior to Drouin et al. The authors of Karp found that lower expression of C5 protein is associated with more severe OVA-induced inflammation in mouse lung (see Figure 1). This discovery is in stark contrast to what a skilled artisan would have expected under the Examiner's interpretation of the Drouin et al. publication. Karp teaches away from the notion that lower levels of C5 protein or activity would reduce the severity of OVA-induced inflammation in mouse lung.

Furthermore, Karp discloses that inhibition of C5aR results in a marked reduction in IL-12 production by monocytes *in vitro* (see Figure 3). IL-12 is a pro-inflammatory cytokine that promotes a T_H1 response over the asthma-associated T_H2 response. The authors of Karp state that "preliminary data from A/J mice in which the wild-type C5 gene has been restored suggest that the T_H2-associated eosinophilic inflammatory response is attenuated in the presence of a functional C5 gene." *See* Karp at page 224, last full paragraph. Therefore, the skilled artisan reading Karp would have believed that C5 was protective against asthma and that inhibition of C5 or C5aR would not be beneficial for treating asthma.

In later publications, the authors of the Drouin et al. reference also taught away from the use of C5 or C5aR inhibition for treating asthma. In 2006, Drs. Scott Drouin and Rick Wetsel (the first and senior authors on the Drouin et al. reference, respectively) co-authored a scientific publication demonstrating a protective role for C5 in allergic airway disease (Drouin et al. (2006) *Am J Respir Crit Care Med* 173:852-857, also re-submitted herewith as Exhibit B; referred to as "Drouin 2006"). Drouin 2006 disclosed that C5-deficient mice developed more severe asthma, including increased

granulocyte infiltration of the lungs, than their C5-sufficient counterparts (see Figure 2). The authors also demonstrated that administration of an anti-C5 antibody (BB5.1) resulted in increased, ***not decreased***, airway hyperresponsiveness (AHR) in acetylcholine-challenged mice (see Figure 7 and the text in the first paragraph of the right-hand column of page 855).

Moreover, Drs. Drouin and Wetsel co-authored an Abstract disclosing a study on AHR and airway inflammation in C5aR knockout mice (Sinha et al. (2008) *Molecular Immunology* 45:4109-4110, Abstract No. O43, also re-submitted herewith as Exhibit C). This Abstract discloses that C5aR knockout mice, as well as wild-type mice treated with a C5aR antagonist, exhibited exacerbated AHR as compared to wild-type or untreated mice, respectively. The authors state that "deficiency or antagonism of the C5aR in a mouse model of pulmonary allergy causes elevated AHR[.]" *See* Sinha et al. at page 4109, paragraph 2.

Thus, contrary to the conclusions in the 4/3/2009 Office Action, the experimental observations in Drouin et al. together with the teachings of the prior art at the time of filing fail to render the claims obvious.

The Office Action dated April 3, 2009 also rejected certain claims as allegedly being unpatentable over Drouin et al. further in view of Fitch et al. The Office Action states that the Drouin et al. reference does not teach the treatment of human subjects or the h5G1.1 antibody, but that Fitch et al. does. It further states that it would have been obvious to a person of ordinary skill in the art to use the h5G1.1 antibody to treat airway inflammation in a human target, such as one with asthma. Applicant respectfully disagrees.

As discussed above, the teachings of Drouin et al. fail to render the instant claims obvious. In addition, the Fitch et al. reference does not cure the deficiencies of Drouin et al. Neither reference teaches the relevance of C5aR to asthma. Thus, the references taken in combination do not teach or suggest all elements of the pending claims.

The Office Action dated April 3, 2009 also rejected certain claims as allegedly being unpatentable over Drouin et al. and further in view of US Patent 4,228,795 ('795 patent) to Babington. The Office Action states that Drouin et al. do not teach a disperser, but that the '795 patent teaches a nebulizer. The Office Action further states that it would have been obvious to a person of ordinary skill in the art to use the nebulizer taught by the '795 patent to administer the anti-C5a antibodies taught by Drouin et al. Applicant respectfully disagrees.

The teachings of Drouin et al. are discussed above, and the '795 patent teaches a nebulizer. Neither reference teaches the relevance of C5aR to asthma. Thus, Drouin et al. do not teach or suggest all elements of the pending claims, and the '795 patent does not make up for these deficiencies. Accordingly, the pending claims are non-obvious over the cited prior art.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P01-102 from which the undersigned is authorized to draw.

Dated: August 12, 2010

Respectfully submitted,

By__/Xuqiong Wu/___
Xuqiong Wu
Registration No.: 55,745
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant